

## REMARKS

This application has been reviewed in light of the Office Action dated July 20, 2010. Claims 1, 3, 6-16, 19, 20 and 22-25 are presented for examination, of which Claims 1 and 22 are in independent form. Claim 21 has been cancelled without prejudice or disclaimer of subject matter and its recitations incorporated into Claims 1 and 22. Claims 3, 6-16, 19 and 24 have been amended as to matters of form only. Claims 1, 20, 22 and 23 have been amended to better define the intended invention. Support for the amendments to Claims 1 and 22 may be found in cancelled Claim 21 and original Claim 23. Support for the amendment to Claims 21 and 23 may be found in original Claims 20 and 22. New Claim 25 has been added to provide Applicants with a better scope of protection. Support for the new claims may be found, *inter alia*, at page 10, lines 5-15, of the subject specification as filed. No new matter has been added. Favorable reconsideration is requested.

Claims 1, 3, 6-16, 19-24 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 3,993,072 (Zaffaroni), U.S. Patent No. 2,962,023 (Chappaz et al.) and U.S. Patent No. 5,972,372 (Saleh et al). Applicants respectfully traverse the rejection.

Prior to discussing the merits of the rejection, Applicants believe it would be helpful to discuss the advantages of the device of this invention. As noted in the specification of the present invention, vaginal rings have been difficult to effectively use, particularly when a daily release rate of a drug on the order of milligrams per day is required, for delivering hydrophilic or relatively large molecular weight (greater than 400 Daltons) drugs. See page 2, line 17 through page 3, line 10, of the subject specification as filed. It is respectfully submitted that the present invention overcomes the aforementioned problem by providing a hydrophobic

elastomeric sheath that is impermeable to the drug so that the drug is released from the hydrophobic elastomeric polymer of the reservoir through the surface area of the reservoir that is exposed to the vaginal environment. This results in a shorter pathway for drug permeation than with conventional sheath-enclosed intravaginal drug delivery devices, where the drug must also diffuse through the sheath.

As amended herein, the claims are specifically directed to an intravaginal drug delivery device (and a related method of drug delivery), wherein the drug has a molecular weight greater than 400 Daltons and is delivered at a pharmaceutically suitable rate. Optionally, the drug is also relatively hydrophilic. This is a significant advancement over the prior art, which neither discloses nor suggests the presently claimed invention.

Zaffaroni evaluates the known approaches to drug delivery devices including enclosing a drug within a single capsule having a polymeric wall or walls through which the drug can pass, for example, by diffusion. Such methods of delivery known in the art generally use a single material, such as silicone rubber polymers, especially polydimethylsiloxane, as the diffusion control membrane. However, high permeability alone, without consideration of release rate controlling properties, can defeat the primary object of an acceptable drug delivery device. With many important drug molecules, such as progesterone, the diffusion rate through a polydimethylsiloxane membrane is great, and often greater than the rate of clearance of the diffused drug from the outer surface of the capsule. In many instances, this results in the rate-limiting step being clearance of the drug through the exterior of the capsule, rather than diffusion through the capsule wall. Clearance rate within the body is difficult to control, as it is subject to frequent change. Accordingly, this known method fails to provide a drug delivery device which

releases a drug at a constant rate over a prolonged time. The drug delivery device disclosed in Zaffaroni is simply not suitable for delivery of many important drug molecules.

Applicants note that the Examiner relies on Examples 1, 16 and 18 of Zaffaroni in finding that Zaffaroni teaches many of the features of the claimed intravaginal drug delivery device. Applicants submit that the reliance is misplaced.

First, Applicants respectfully submit that it is inappropriate to equate the implant device of Example 1 with the intrauterine device of Example 16 or the vaginal ring device of Example 18. Zaffaroni uses the term “drug delivery device” to embrace tablets for oral delivery (Figure 3), devices for anal delivery (Figure 4), implants (Figure 5), intrauterine devices (Figures 6 and 7), and vaginal devices (Figure 8). The Examiner will appreciate that the peroral tablet of Figure 3 is intended to be suitable for oral administration while the device of Figure 4 is intended for anal administration. Those skilled in the art would have understood that not specifying vaginal delivery as an option for Example 1 indicates that it is not necessarily suitable for that purpose, bearing in mind the wide range of drug delivery devices taught by Zaffaroni.

Second, the drug in Example 1 of Zaffaroni is progesterone. Progesterone has a molecular weight of 314.5 Daltons, whilst the presently amended claims require that the drug have a molecular weight greater than 400 Daltons. Accordingly, Zaffaroni fails to suggest or disclose a drug delivery device or method of delivery, wherein the drug has a molecular weight greater than 400 Daltons and is delivered at a pharmaceutically suitable rate.

In addition, as to Claims 19 and 24, Zaffaroni teaches a uterine release of 10 to 200µg per day of progesterone (column 20, lines 15-21). Zaffaroni neither discloses nor suggests an intravaginal drug delivery device having a daily release rate of the drug in the order of milligrams per day.

Third, Zaffaroni teaches, at column 2, lines 19- 41, that many important drugs, including progesterone, diffuse quickly through a polydimethylsiloxane sheath, so much that diffusion through the sheath is not the rate-limiting step. Accordingly, Zaffaroni teaches that polydimethylsiloxane sheathes, being hydrophobic elastomeric sheathes, are disadvantageous, thereby teaching away from the present invention.

Lastly, Zaffaroni aims to ensure that drug release from its device is controlled by the drug release rate-controlling medium in the pores. Zaffaroni teaches those of ordinary skill in the art to restrict pore size to 2 to 3 times the molecular radius of the drug molecule and discourages using a pore size outside that range. Examples 15 and 17 disclose an average pore diameter of 45 and 24 angstroms, respectively, for progesterone. Example 3 discloses an average pore size of 24 angstroms for hydrocortisone and Example 4 discloses a pore size of 0.45 microns for hydrocortisone alcohol. Examples 12 and 13 disclose pores having a diameter of 40 and 50 angstroms for phenylglycodol. There is nothing in Zaffaroni that discloses or suggests using pores with a diameter in the range of about 0.5 to 6.5 mm, as presently claimed.

As acknowledged by the Examiner, Zaffaroni does not disclose that the pore or opening has a diameter in the range of about 0.5 to 6.5 mm or that the total surface area of the reservoir exposed to the vaginal environment through the one or more holes or openings, when in use, is in a range of 1 to 750mm<sup>2</sup>. In addition, Zaffaroni fails to teach or suggest delivery of a drug having a molecular weight greater than 400 Daltons at a pharmaceutically suitable rate, and, optionally, that the drug is relatively hydrophilic.

The Examiner alleges that it would have been obvious to one of skill in the art to combine Chappaz with Zaffaroni. However, Chappaz, like Zaffaroni, does not teach or suggest delivery of a drug having a molecular weight greater than 400 Daltons at a pharmaceutically

suitable rate. Instead, Chappaz discloses a medicating device comprising a container for liquid, gelatinous or particulate solid medicating substance (column 1, lines 15 – 18), whereby the container must be thermally stable to resist deformation or warping (column 1 lines 59-60). It is essential that the container have sufficient rigidity to prevent complete elastic collapse so that the bulk of the drug isn't quickly forced out of the container (column 2, lines 1-7). Example 1 of Chappaz exemplifies that the device is filled with a medicating cream that melts at body temperature and exudes slowly, but continuously, through the perforations in the container wall. Further, Chappaz teaches in Example 1 that various medicaments such as creams, jellies, liquids and even powder may be enclosed within the container.

As the Examiner will appreciate and, as is taught at page 10, lines 5-15 of the subject specification as filed, for drug delivery from conventional intravaginal drug delivery devices, which are fully surrounded by rate-controlling sheaths, drugs are usually incorporated into the reservoir at sufficiently high concentrations such that most of the drug is present in the solid state. Before release can occur, individual molecules of the dispersed active drug(s) within the reservoir must first detach themselves from their crystal lattice, dissolve into the surrounding reservoir carrier system, diffuse to the surface of the reservoir and then diffuse through the sheath to the surface of the device.

The present invention addresses the problem of delivering a drug having a molecular weight greater than 400 Daltons at a pharmaceutically suitable rate from an intravaginal drug delivery device by shortening the subsequent pathways of diffusion for drug permeation compared with conventional sheath-enclosed intravaginal drug delivery devices, where the drug must also diffuse through the sheath.

Chappaz achieves drug delivery without requiring the drug to diffuse through the reservoir. In the device of Chappaz, the entire “core” (drug and reservoir) is released through holes in an applicator. This is in contrast to the present application, wherein the reservoir comprising the hydrophobic elastomeric polymer, in which the drug is dispersed, remains intact and in place. In the present invention, only the drug is released into the vaginal environment.

Applicants respectfully submit that the combination of Zaffaroni and Chappaz fails to render the present invention obvious. Zaffaroni teaches the disadvantages of enclosing the drug within a single capsule having a polymeric wall or walls through which the drug can pass, for example, by diffusion and Chappaz teaches exudation of the drug and reservoir, together, through the container wall. Neither reference teaches an intravaginal delivery device, or method therefore, for delivering a drug having a molecular weight greater than 400 Daltons at a pharmaceutically suitable rate, as presently claimed.

Saleh fails to remedy the deficiencies of Zaffaroni and Chappaz. Salah addresses the problem of controlling an initial burst of steroid release that may be associated with nausea and vomiting. Saleh solves this problem and provides a vaginal ring that does not cause nausea and vomiting by preparing a core containing the drug kept separate from a vaginal ring body having at least one hollow internal channel to receive the core and by assembling the core within the vaginal ring body within about four days or less prior to use. This is so that, upon administration of the assembled vaginal ring, there is no (i.e., negligible) initial burst of the drug that would otherwise tend to cause undesirable side effects such as nausea or vomiting.

Saleh does not teach or suggest how to deliver a drug having a molecular weight greater than 400 Daltons at a pharmaceutically suitable rate from an intravaginal drug delivery device. Instead, Saleh concerns itself with reducing an initial burst effect for vaginal rings

containing a progestin (Nestorone, molecular weight of 370.48) and ethinyl estradiol (molecular weight of 296.4).

Further, Applicants respectfully suggest that Saleh, in its assembled vaginal ring, teaches away from having its core exposed to the vaginal environment, as recited in the claimed invention. Firstly, Saleh's purpose to reduce an initial burst of drug release from the core is completely inconsistent with directly exposing the core to the vaginal environment. Secondly, Saleh requires that the vaginal ring body have at least one hollow internal channel and a sealant that may be used to separate the core from the exterior environment so as to prevent passage or diffusion of the drug from the core directly to the exterior environment. The term "internal" is defined as no portion of the core is exposed to or is in contact with the outer surface of the ring body once the vaginal ring is fully assembled, such that, when administered, the drug diffuses from the core directly into the tissue of the subject (column 6, lines 6-12). Further, at column 6, line 62 to column 7, line 2, it is taught that a sealant is used to close the channel after core placement and to minimize diffusion of the drug through the ends of the core. Figures 4A, 4B and 4C illustrate the assembly of the vaginal ring. As evident from Figure 4C and from the accompanying text at column 6, lines 44-45, a sealant 49 prevents the core from being in direct contact with the vaginal environment. Similarly, in Figure 5, the cores are each sealed with sealant 59.

The Examiner has relied on Saleh to teach a polymer impregnated with a drug that goes inside a sheath with holes. However, the vaginal ring body of Saleh does not comprise a reservoir containing at least one drug dispersed in a hydrophobic elastomeric polymer and a hydrophobic elastomeric sheath discontinuously surrounding the reservoir. Instead, the vaginal

ring body of Saleh is a single entity, having no holes and no direct exposure to the vaginal environment.

Since the purpose of Saleh is to control nausea and vomiting resulting from initial bursts of the drug, it is clear that Saleh teaches away from the presently claimed invention, which provides a reservoir with a surface area directly exposed to the vaginal environment in a range of 1 to 750mm<sup>2</sup>. Therefore, it is respectfully submitted that Saleh would not be combined with the other cited references to arrive at the presently claimed invention.

Applicants respectfully submit that Zaffaroni, Chappaz and Saleh, alone or in any permissible combination, fail to disclose or suggest each and every feature of the claimed invention and fail to render the present invention obvious for at least the reasons set forth above. Accordingly, Applicants respectfully request withdrawal of the 103 rejection.

In view of the foregoing remarks, favorable reconsideration and passage to issue is earnestly requested. Should the Examiner believe that issues remain outstanding, the Examiner is respectfully requested to contact Applicants' undersigned attorney in an effort to resolve such issues and advance the case to issue.

In view of the foregoing amendments and remarks, Applicants respectfully request favorable reconsideration and early passage to issue of the present application.

Applicants' undersigned attorney may be reached in our New York Office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address listed below.

Respectfully submitted,

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